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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/854,825	05/12/97	CHISARI	F	329368-101C0

HM11/0316

LEYDIG VOIT AND MAYER
TWO PRUDENTIAL PLAZA
180 NORTH STETSON SUITE 4900
CHICAGO IL 60601-6780

EXAMINER	
PARKIN, J	

ART UNIT	PAPER NUMBER
1648	51

DATE MAILED: 03/16/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/854,825	Chisari et al.
Examiner	**Group Art Unit**
Jeffrey S. Parkin, Ph.D.	1648

☒ Responsive to communication(s) filed on *10 Nov 1997*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *22-59* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *22-59* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Detailed Office Action

Status of the Claims

1. Acknowledgement is hereby made of the Preliminary Amendment filed 10 November, 1997, wherein claims 10-19 and 21 were canceled without prejudice or disclaimer and new claims 22-59 submitted. Claims 22-59 are pending in the instant application.

35 U.S.C. § 120

2. If applicant desires priority under 35 U.S.C. § 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of non-provisional application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application. Applicants are advised that the '650 application has matured into U.S. Patent No. 5,709,995. Appropriate correction is required.

Information Disclosure Statement

3. The information disclosure statement filed 17 November, 1997, has been placed in the application file and the information referred to therein has been considered.

Drawings

4. The drawings filed in this application are objected to by the Draftsperson under 37 C.F.R. §§ 1.84 or 1.152 as indicated. These drawings are acceptable for examination purposes only. Formal

drawings with the appropriate corrections will be required when the application is allowed.

35 U.S.C. § 112, First Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 22-57 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Claims 22-26, 28, 30, 32, 34, 36, 38, 40, and 42 are drawn toward isolated hepatitis C virus (HCV) cytotoxic T-lymphocyte (CTL) peptides differing no more than about 20% from the disclosed parent sequences (e.g., SEQ ID Nos.: 1-3, 26, 28, 34, 35, 42, and 54). Claims 44-51 are directed toward immunogenic compositions comprising these peptides. Claims 52-55 are drawn toward methods for stimulating HCV-specific CTL responses in mammals employing the aforementioned peptides. Claims 56 and 57 are drawn toward methods of detecting HCV-specific CTL employing the claimed peptides.

The disclosure details the identification of seven HCV CTL epitopes corresponding to regions of the core (e.g., amino acids 131-140 and 178-187), NS3 (e.g., amino acids 1169-1177 and 1406-1415), NS4 (e.g., amino acids 1789-1797 and 1807-1816), and NS5 (e.g., amino acids 2252-2260) antigens (refer to pages 52 and 55 of the specification). These peptides were used to identify HCV-specific CTL responses in HCV-infected patients and some were employed in the generation of murine HCV-specific CTL.

The claimed invention is directed toward peptides that differ by no more than "about 20%" from parental HCV sequences. As such, the claim language encompasses peptides containing single or multiple amino acid substitutions, deletions, or additions. The disclosure does not support the breadth of the claimed invention as follows:

(1) The disclosure fails to provide sufficient guidance or direction pertaining to acceptable amino acid replacements, additions, or deletions the CTL epitope that will retain the MHC-restricted CTL response. The prior and present art teach that mutations in CTL epitopes adversely affect binding to the appropriate MHC Class I molecule (Smith *et al.*, 1997; Bertoletti *et al.*, 1994; Johnson *et al.*, 1992; Couillin *et al.*, 1995; and, Hahn *et al.*, 1992). Additionally, applicants themselves state (refer to page 5 of the disclosure) that "At the present time, it is difficult to predict from the sequence of an antigenic protein how the protein will be processed and which peptide portions will bind HLA class I molecules and be presented to CTL's. Binding motifs have been predicted for some HLA class I molecules based on sequence analysis of peptides eluted from these molecules. . . However, not all peptides that match the motif will be recognized as CTL-recognizable epitopes. Moreover, even of the peptides that are processed and bind to HLA class I molecules, identifying which ones will contain CTL-recognizable epitopes is not yet predictable." Without any prior instruction, which amino acid substitutions could one practicing the invention introduce directly into the CTL epitope and still retain an MHC Class I-restricted CTL response?

(2) The disclosure fails to provide sufficient guidance or direction concerning the affects of amino acid substitutions, additions, or deletions on sequences flanking the disclosed CTL epitopes. The prior art teaches that flanking amino acid residues critically influence the degree of peptide processing and presentation (Del Val *et al.*, 1991; Hahn *et al.*, 1992; and, Eisenlohr *et al.*, 1992). As

described in the preceding paragraph, it is difficult to predict what amino acid sequences are required for proper peptide processing by the host and how they influence CTL recognition and lysis. Eisenlohr *et al.* (1992) reported that CTL epitopic flanking amino acid residues were critical for the efficient processing and presentation of antigen to CTL. Flanking sequences were capable of either enhancing or abrogating peptide processing and recognition. Hahn *et al.* (1992) disclosed that a single amino acid substitution immediately flanking the recognized CTL epitope significantly curtailed CTL-mediated cell lysis. Additional CTL studies performed by Del Val *et al.* (1991) documented that "residues that directly flank the antigenic sequence in a protein critically influence the amount of naturally processed and presented antigenic peptide." Moreover, the art also teaches that mutations in CTL epitopes adversely affect extracellular antigen processing by altering the trimming of flanking residues in longer sequences and influencing the susceptibility of optimal epitopes to proteolytic degradation (Smith *et al.*, 1997; Del Val *et al.*, 1991; Eisenlohr *et al.*, 1992). In the absence of further guidance how would one practicing the invention reasonably predict which amino acid substitutions, additions, and/or deletions, will result in retention of the desired immunologic properties of any given peptide? (3) The disclosure fails to teach which, of the myriad number of peptides encompassed by the claim language, can reasonably be expected to undergo efficient processing and presentation. The art teaches that the presence of an MHC class I binding motif in a peptide is not sufficient to confer binding to the appropriate class I molecule (Nayersina *et al.*, 1993; Bertoletti *et al.*, 1994; Couillin *et al.*, 1995; and, Eisenlohr *et al.*, 1992). However, the specification fails to provide appropriate guidance pertaining to this point and further suggests that the skilled artisan cannot reasonably make this determination (see preceding paragraph and page 5 of the disclosure).

(4) The disclosure fails to provide adequate guidance pertaining to the immunological properties of any given putative CTL-epitope containing peptide. The art teaches that the capacity of a putative CTL epitope to bind to a class I molecule does not mean that the epitope will be immunogenic (Nayersina *et al.*, 1993; Couillin *et al.*, 1995; and, Eisenlohr *et al.*, 1992). The specification is silent concerning this caveat.

(5) The disclosure fails to provide any guidance concerning the effects of MHC Class I polymorphisms upon CTL epitope recognition and processing. Hansen *et al.* (1993) disclose the presence of 41 different alleles for the HLA-A locus, 61 for the HLA-B locus, and 18 for the HLA-C locus. Studies by Koziel *et al.* (1993) demonstrated that different HLA-restricted cloned cell lines (obtained from HCV-infected patients) recognized divergent CTL epitopes. Furthermore, the applicants reported (pp. 51-52) that only 4 out of 8 patients with the same HLA haplotype (e.g., A2.1) generated a CTL response to the aforementioned HCV oligopeptides. Monaco (1992) further discusses polymorphisms external to the MHC locus in the low molecular mass polypeptide (LMP) complex and transporter genes that may also result in the presentation of different epitopes of the same antigen to the T-cell repertoire. Without further instruction, which of the disclosed CTL epitopes could one practicing the invention use to elicit a CTL response in individuals with different or similar MHC Class I haplotypes? Which amino acid substitutions in the CTL epitope or flanking regions would result in retention of the CTL response in patients with different MHC Class I specificities?

Moreover, the claims (52-55) also encompass the stimulation of CTL responses in humans and other mammals, presumably to confer protective or therapeutic responses against HCV infection. In addition to the aforementioned caveats pertaining to the selection of a suitable peptide, a number of additional factors would preclude the skilled artisan from practicing the invention as broadly as claimed.

The art teaches that virally infected patients contain CTL epitopic variants with reduced HLA and T cell receptor binding capacities (Bertoletti *et al.*, 1994 and Couillin *et al.*, 1995). Furthermore, natural sequence variation in viruses, particularly in CTL epitopes, results in the generation of immune resistant viruses (Bertoletti *et al.*, 1994; Johnson *et al.*, 1992; and, Couillin *et al.*, 1995). Finally, the art also teaches that HCV-specific CTL may actually contribute to liver disease pathogenesis in chronically infected patients (Rehermann *et al.*, 1996). Thus, it is not readily manifest that even upon identification of the appropriate candidate peptide, that said peptide would generate HCV-specific CTL capable of providing an ameliorative response.

The prior art clearly details a number of caveats pertaining to the identification, selection, and use of CTL epitopes and these can be summarized as follows:

(1) The art teaches that mutations in CTL epitopes adversely affect binding to the appropriate MHC Class I molecule.

(2) The prior art teaches that flanking amino acid residues critically influence the degree of peptide processing and presentation.

(3) The art teaches that the presence of an MHC class I binding motif in a peptide is not sufficient to confer binding to the appropriate class I molecule.

(4) The art teaches that the capacity of a putative CTL epitope to bind to a class I molecule does not mean that the epitope will be immunogenic.

(5) The art teaches that virally infected patients contain CTL epitopic variants with reduced HLA and T cell receptor binding capacities.

(6) The art teaches that natural sequence variation in viruses, particularly in CTL epitopes, results in the generation of immune resistant viruses.

(7) The art teaches that HCV-specific CTL may actually contribute to liver disease pathogenesis in chronically infected patients. Accordingly, when the aforementioned factors are considered *in toto*, it would clearly require undue experimentation to practice the invention as presently claimed. Applicants may obviate this rejection by directing the claim language toward those specific peptides that contain demonstrable HCV CTL epitopes and the requisite immunogenicity to stimulate high-titers of HCV-specific CTL.

7. Claims 58 and 59 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 58 and 59 are drawn toward pharmaceutical compositions comprising HCV-derived peptides. The term pharmaceutical has an art-recognized definition and pertains to the use of medicinal drugs to treat disease (refer to Dorland's medical dictionary, 1988, pp. 1271-1272; *In re Gardner*, 166 U.S.P.Q. 138-142 (1970 C.C.P.A.); and, *Ex parte Skuballa*, 12 U.S.P.Q.2d 1570 (1989 Bd. Pat. App. Int.)). As such, the claimed peptides would presumably be employed in the prevention or treatment of HCV infection, predominantly in humans since this represents the natural host.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments. The board disclosed these considerations in *Ex parte Forman* as follows:

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the

> art: *Ansul Co. v. Uniroyal, Inc.*, supra. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. The factors to be considered have been summarized as **the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art** and **the breadth of the claims.** *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965); *In re Colianni, supra.*

As set forth in the preceding arguments pertaining to claims 22-57, a number of pragmatic scientific caveats would preclude the skilled artisan from practicing the claimed invention as follows:

(1) The art teaches that mutations in CTL epitopes adversely affect binding to the appropriate MHC Class I molecule.

(2) The prior art teaches that flanking amino acid residues critically influence the degree of peptide processing and presentation.

(3) The art teaches that the presence of an MHC class I binding motif in a peptide is not sufficient to confer binding to the appropriate class I molecule.

(4) The art teaches that the capacity of a putative CTL epitope to bind to a class I molecule does not mean that the epitope will be immunogenic.

(5) The art teaches that virally infected patients contain CTL epitopic variants with reduced HLA and T cell receptor binding capacities.

(6) The art teaches that natural sequence variation in viruses, particularly in CTL epitopes, results in the generation of immune resistant viruses.

(7) The art teaches that HCV-specific CTL may actually contribute to liver disease pathogenesis in chronically infected patients.

Moreover, the use of the claimed peptides as therapeutics provides

additional constraints that would preclude the skilled artisan from practicing the invention.

(1) The disclosure fails to provide sufficient guidance demonstrating that a vigorous HCV-specific CTL response can be generated in humans, or other mammals, that will result in amelioration of the clinical sequelae associated with HCV infection. As previously set forth, Rehermann *et al.* (1996), observe that patients chronically infected with HCV develop HCV-specific CTL, but these CTL response are unable to clear the infection or produce any immediate salubrious effects. The authors concluded (refer to Discussion, page 1439) that "these results and the published database suggest that **the CTL response probably contributes to disease pathogenesis but is not vigorous enough to eradicate the virus during chronic HCV infection in most patients.**"

(2) The disclosure fails to identify the correlates of protective immunity as it pertains to HCV infection. Koziel *et al.* (1997), Koff (1993), and Prince (1994) review some of the hurdles associated with developing adoptive immunotherapy involving HCV-specific CTL to combat HCV infection. They note that the correlates of protective immunity remain to be elucidated. Patients, often vigorously, develop HCV-specific CTL responses, but these response are often inadequate and incapable of clearing the virus or providing any substantial ameliorative effects. A number of factors contribute toward this inadequate immune response including the presence of HCV variants that elude immune surveillance, the presence of variant HCV CTL epitopes with altered antigen processing, transport, and presentation properties, and allelic MHC variation within any given patient population. Moreover, Koff (1993) adds that "the general failure to identify a neutralizing, protective humoral immune response in HCV infection coupled with the data described by Farci et al. represent an awesome constellation of impediments to the development of a HCV vaccine."

(3) The disclosure fails to provide appropriate *in vitro* systems for the propagation of HCV and assays for the study of infection of cytopathic effects. In order to identify putative therapeutic compounds, the skilled artisan must first have the requisite *in vitro* systems with which to propagate the infectious agent of interest and assays to determine the potential antiviral activity of any given compound. The art teaches that these systems and assays are not available to the virologist pursuing HCV antivirals (Koff, 1993 and Prince, 1994). As Koff (1993) concludes, "The list of obstacles to the development of a hepatitis C vaccine is becoming formidable. Failure to propagate HCV in tissue culture, the absence of simple in vitro assays for infection or cytopathic effects . . . are well known but not insurmountable issues."

(4) The disclosure fails to provide adequate testing of the proposed pharmaceuticals in an art-recognized animal model. Following the preliminary screening of putative antiviral candidates in *in vitro* assays, the skilled artisan generally employs a suitable animal model to further address concerns that are not evident or addressed by *in vitro* screening assays (i.e., pharmacological properties of the putative therapeutic). However, the art teaches that such models are not available to the skilled artisan trying to develop an anti-HCV compound (Koff, 1993). As Koff (1993) reports, "The list of obstacles to the development of a hepatitis C vaccine is becoming formidable . . . and the lack of a suitable small-animal model are well known but not insurmountable issues." Thus, when the aforementioned factors are considered *in toto*, it would clearly require undue experimentation to practice the invention as presently claimed.

35 U.S.C. § 112, Second Paragraph

8. Claims 22-59 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which applicant regards as the invention. Two separate requirements are set forth under this statute: (1) the claims must set forth the subject matter that applicants regard as their invention; and (2) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.

The claims are drawn toward or include peptides that differ "no more than about 20% from" peptides having the disclosed SEQ ID NOS. The recitation "about 20%" is vague and indefinite because it is not readily manifest which peptides would be included in this recitation. Would peptides displaying 25% be encompassed by the claim language? Would peptides displaying 21% be encompassed by the claim language? Absent further clarification, the metes and bounds of the patent protection desired cannot be ascertained. Applicants may obviate this rejection by simply stating a peptide that differs by no more "than 20%."

Moreover, the reference to differences in sequence is also vague and indefinite. It is not readily manifest if applicants are referring to sequence identities or homologies. These terms each have art-recognized meanings. The term "homology" is qualitative and implies that two sequences possess a common evolutionary origin (Reeck *et al.*, 1987; Lewin, 1987; and Boswell *et al.*, 1988). This term is often employed when scientists are referring to evolutionary relationships (i.e., have two sequences in question evolved from a common ancestor). Conversely, when making direct quantitative comparisons, the term similarity should be employed. This denotes a direct quantitative relationship between two sequences (i.e., amino acid sequence A shares 90% sequence identity with amino acid sequence B). It would appear from reading the specification that the applicants are actually referring to the sequence similarity, or genetic identity, of different amino acid or nucleotide sequences. When referring to sequence similarities appropriate statistical

documentation should be provided (i.e., the precise comparative algorithm and search parameters employed) since the art does not recognize a single given method of making these comparisons. Moreover, the precise search parameters to be employed are also required because these can vary within a single algorithm, thereby providing disparate results. Additionally, the following terms should be employed: a level or degree of similarity/identity; an alignment with optimized similarity; a percentage of positional identity in an alignment; the probability associated with a particular alignment. Appropriate correction of the claim language is required.

Statutory Type Double Patenting, 35 U.S.C. § 101

9. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. § 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor . . ." Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S.P.Q. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 U.S.P.Q. 330 (C.C.P.A. 1957); and *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970).

A statutory type (35 U.S.C. § 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer **cannot** overcome a double patenting rejection based upon 35 U.S.C. § 101.

10. Claims 27, 29, 31, 33, 35, 37, 39, 41, and 43 are rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 2-10, respectively, of prior U.S. Patent No. 5,709,995. This is a double patenting rejection. The claims of the '995 patent recite isolated peptides having the same SEQ ID NOS.: as those

isolated peptides currently claimed by applicants.

Non-statutory Double Patenting

11. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum*, 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman*, 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

12. Claims 22-26, 28, 30, 32, 34, 36, 38, 40, 42, and 44-59 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 11-33 of U.S. Patent No. 5,709,995 (refer to Appendix for claim listing). Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the '995 application are directed toward isolated peptides, pharmaceutical compositions, and methods of use having the same SEQ ID NOS. as those claimed by applicants in this application. The claims of the instant application are directed toward isolated peptides varying by no more

than about 20% and as such, encompass the claims of the '995 application.

Correspondence

13. The Art Unit location of your application in the Patent and Trademark Office has changed. To facilitate the correlation of related papers and documents for this application, all future correspondence should be directed to **art unit 1648.**

14. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 305-7939. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

15. Any inquiry concerning this communication should be directed to **Jeffrey S. Parkin, Ph.D.**, whose telephone number is **(703) 308-2227.** The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, **Donald E. Adams, Ph.D.**, can be reached at **(703) 308-0570.** Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

23 February, 1998

LAURIE SCHEINER
PRIMARY EXAMINER

Appendix A

L3 ANSWER 1 OF 1 USPATFULL
1998:6917 Hepatitis C virus-derived peptides capable of inducing cytotoxic T lymphocyte responses.
Chisari, Francis V., Del Mar, CA, United States
Cerny, Andreas, La Jolla, CA, United States
The Scripps Research Institute, La Jolla, CA, United States (U.S. corporation)
US 5709995 980120
APPLICATION: US 94-214650 940317 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. A peptide having the sequence of ADLMGYIPLV (Core.sub.131-140 ; SEQ ID NO:1), DMLGYIPLV (Core.sub.132-140 ; SEQ ID NO:54), LLALLSCLTV (Core.sub.178-187 ; SEQ ID NO:2), QLRRHIDLLV (E1.sub.257-266 ; SEQ ID NO:3), LLCPAGHAV (NS3.sub.1169-1177 ; SEQ ID NO:26), KLVALGINAV (NS3.sub.1406-1415 ; SEQ ID NO:28), SLMAFTAAV (NS4.sub.1789-1797 ; SEQ ID NO:34), LLFNILGGWV (NS4.sub.1807-1816 ; SEQ ID NO:35), or ILDSFDPLV (NS5.sub.2252-2260 ; SEQ ID NO:42).

2. The peptide of claim 1, wherein the peptide has the sequence of ADLMGYIPLV (Core.sub.131-140 ; SEQ ID NO:1).

3. The peptide of claim 1, wherein the peptide has the sequence of DMLGYIPLV Core.sub.132-140 ; SEQ ID NO:54).

4. The peptide of claim 1, wherein the peptide has the sequence of LLALLSCLTV (Core.sub.178-187 ; SEQ ID NO:2).

5. The peptide of claim 1, wherein the peptide has the sequence of QLRRHIDLLV (E1.sub.257-266 ; SEQ ID NO:3).

6. The peptide of claim 1, wherein the peptide has the sequence of LLCPAGHAV (NS3.sub.1169-1177 ; SEQ ID NO:26).

7. The peptide of claim 1, wherein the peptide has the sequence of KLVALGINAV (NS3.sub.1406-1415 ; SEQ ID NO:28).

8. The peptide of claim 1, wherein the peptide has the sequence of SLMAFTAAV (NS4.sub.1789-1797 ; SEQ ID NO:34).

9. The peptide of claim 1, wherein the peptide has the sequence of LLFNILGGWV (NS4.sub.1807-1816 ; SEQ ID NO:35).

10. The peptide of claim 1, wherein the peptide has the sequence of ILDSFDPLV (NS5.sub.2252-2260 ; SEQ ID NO:42).

11. An immunogenic composition comprising a peptide having the sequence of ADLMGYIPLV (Core.sub.131-140 ; SEQ ID NO:1), DMLGYIPLV (Core.sub.132-140 ; SEQ ID NO:54), LLALLSCLTV (Core.sub.178-187 ; SEQ ID NO:2), QLRRHIDLLV (E1.sub.257-266 ; SEQ ID NO:3), LLCPAGHAV (NS3.sub.1169-1177 ; SEQ ID NO:26), KLVALGINAV (NS3.sub.1406-1415

; SEQ ID NO:28), SLMAFTAAV (NS4.sub.1789-1797 ; SEQ ID NO:34), LLFNILGGWV (NS4.sub.1807-1816 ; SEQ ID NO:35), or ILDSFDPLV (NS5.sub.2252-2260 ; SEQ ID NO:42).

12. The immunogenic composition of claim 11, wherein the immunogenic composition further comprises a label selected from the group consisting of a radioactive label, an enzymatic label, and a fluorescent label.

13. The immunogenic composition of claim 11, wherein the immunogenic composition further comprises a solid matrix.

14. The immunogenic composition of claim 11, wherein the immunogenic composition further comprises a carrier molecule.

15. The immunogenic composition of claim 14, wherein the carrier molecule comprises a protein or an immunogenic lipid.

16. The immunogenic composition of claim 11, wherein the immunogenic composition further comprises a T-helper lymphocyte epitope.

17. The immunogenic composition of claim 11, wherein the immunogenic composition further comprises an additional peptide.

18. The immunogenic composition of claim 17, wherein the additional peptide has a sequence of KLVALGINAV (NS3.sub.1406-1415 ; SEQ ID NO:28).

19. A method of stimulating a cytotoxic T-lymphocyte response to a hepatitis C viral immunogen, comprising contacting an HLA class I-restricted cytotoxic T lymphocyte with a composition comprising a peptide having the sequence of ADLMGYIPLV (Core.sub.131-140 ; SEQ ID NO:1), DLMGYIPLV (Core.sub.132-140 ; SEQ ID NO:54), LLALLSCLTV (Core.sub.178-187 ; SEQ ID NO:2), QLRRHIDLLV (E1.sub.257-266 ; SEQ ID NO: 3), LLCPAGHAV (NS3.sub.1169-1177 ; SEQ ID NO:26), KLVALGINAV (NS3.sub.1406-1415 ; SEQ ID NO:28), SLMAFTAAV (NS4.sub.1789-1797 ; SEQ ID NO:34), LLFNILGGWV (NS4.sub.1807-1816 ; SEQ ID NO:35), or ILDSFDPLV (NS5.sub.2252-2260 ; SEQ ID NO:42).

20. The method of claim 19, wherein the contacting occurs in a mammal.

21. The method of claim 20, wherein the mammal is free of HCV disease, is a carrier of HCV, or is afflicted with HCV disease.

22. The method of claim 19, wherein the contacting occurs in vitro.

23. A method of detecting cytotoxic T cells that respond to a T cell epitope of hepatitis C virus, the method comprising the steps of: (a) preparing HLA class I-restricted cytotoxic T cells; (b) preparing HLA class I-matched and -mismatched target cells; (c) contacting separately matched and mismatched target cells with a composition comprising a peptide having the sequence of ADLMGYIPLV (Core.sub.131-140 ; SEQ ID NO:1), DMLGYIPLV (Core.sub.132-140 ; SEQ ID NO:54); LLALLSCLTV (Core.sub.178-187 ; SEQ ID NO:2),

QLRRHIDLLV (E1.sub.257-266 ; SEQ ID NO:3), LLCPAGHAV (NS3.sub.1169-1177 ; SEQ ID NO:26), KLVALGINAV (NS3.sub.1406-1415 ; SEQ ID NO:28), SLMAFTAAV (NS4.sub.1789-1797 ; SEQ NO:34), LLFNILGGWV (NS4.sub.1807-1816 ; SEQ ID NO:35), or ILDSFDPLV (NS5.sub.2252-2260 ; SEQ ID NO:42); (d) combining the cytotoxic T cells separately with the matched and mismatched target cells; and (e) measuring cytolysis.

24. The method of claim 23, wherein the cytotoxic T cells are combined with HLA class I-matched lymphocytes.

25. A pharmaceutical composition comprising a peptide having the sequence of ADLMGYIPLV (Core.sub.131-140 ; SEQ ID NO:1), DLMGYIPLV (Core.sub.132-140 ; SEQ ID NO:54), LLALLSCLTV (Core.sub.178-187 ; SEQ ID NO:2), QLRRHIDLLV (E1.sub.257-266 s; SEQ ID NO:3), LLCPAGHAV (NS3.sub.1169-1177 ; SEQ ID NO:26), KLVALGINAV (NS3.sub.1406-1415 ; SEQ ID NO:28), SLMAFTAAV (NS4.sub.1789-1797 ; SEQ ID NO:34, LLFNILGGWV (NS4.sub.1807-1816 ; SEQ ID NO:35), or ILDSFDPLV (NS5.sub.2252-2260 ; SEQ ID NO:42), and a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of claim 25, wherein the peptide has the sequence of DMLGYIPLV (Core.sub.132-140 ; SEQ ID NO:54).

27. The pharmaceutical composition of claim 25, wherein the peptide has the sequence of LLALLSCLTV (Core.sub.178-187 ; SEQ ID NO:2).

28. The pharmaceutical composition of claim 25, wherein the peptide has the sequence of QLRRHIDLLV (E1.sub.257-266 ; SEQ ID NO:3).

29. The pharmaceutical composition of claim 25, wherein the peptide has the sequence of LLCPAGHAV (NS3.sub.1169-1177 ; SEQ ID NO:26).

30. The pharmaceutical composition of claim 25, wherein the peptide has the sequence of KLVALGINAV (NS3.sub.1406-1415 ; SEQ ID NO:28).

31. The pharmaceutical composition of claim 25, wherein the peptide has the sequence of SLMAFTAAV (NS4.sub.1789-1797 ; SEQ ID NO:34).

32. The pharmaceutical composition of claim 25, wherein the peptide has the sequence of LLFNILGGWV (NS4.sub.1807-1816 ; SEQ ID NO:35).

33. The pharmaceutical composition of claim 25, wherein the peptide has the sequence of ILDSFDPLV (NS2.sub.2252-2260 ; SEQ ID NO:42).